

•In this issue•

The first paper in this issue is a review of the use of antipsychotic medications in the treatment of depressive conditions.^[1] Previously, combined therapy with antidepressants and antipsychotics was largely a time-limited alternative in patients whose depressive symptoms were complicated by delusions and hallucinations. Several trends over the last two decades have gradually changed the clinical attitude about this issue. The rapid increase in the diagnosis of Schizoaffective Disorder, a phenomenon that has not happened in China but is clearly evident in the United States, has blurred the line between depressive and psychotic disorders. The widespread replacement of atypical antipsychotics for the first generation antipsychotics has, perhaps prematurely, decreased concerns about the severe side effects associated with the use of antipsychotic medication. And increased attention to the substantial minority of persons with depressive disorders who get limited benefit from antidepressant treatment has intensified the search for adjunctive treatments that can improve clinical outcomes for these individuals. The biological rationale for using antipsychotics with depression is their presumed effect in the regulation of monoamine, glutamate, *gamma*-aminobutyric acid (GABA), cortisol, and neurotrophic factors. Drug regulatory agencies have started to approve some of the new antipsychotic medications such as quetiapine, aripiprazole and olanzapine as adjunctive treatment (and, in some cases, as monotherapy) for treatment-resistant depression. However, the potential benefits of the long-term use of antipsychotics during the maintenance phase of treatment for depression remain unknown and there are substantial risks associated with chronic use of these medications, particularly in elderly patients. As always, clinicians need to carefully monitor the risk-benefit ratio of combined antipsychotic and antidepressant therapy for each individual patient and monitor changes in this balance over the course of treatment.

The first original article^[2] describes the first known application of a test of high-level cognitive functioning – error-related negativity (ERN) – in patients with a history of heroin addiction. With over a million registered heroin users in China (and an unknown number of unregistered users) it is clear that illicit drug use is a growing problem in the country, as confirmed in the recent report of the 1990 to 2010 changes in the burden of disease in China.^[3] Despite the growing public health importance of drug abuse in China, there has been relatively little research about these problems, probably because most such individuals are confined to compulsory residential centers run by the police. The current study enrolled 20 male subjects from a government-run drug rehabilitation

center with a history of heroin dependence who had been drug-free for 4-10 months. These individuals were administered Erikson flanker tasks to provoke ERN waves on the 32-electrode electroencephalograph (EEG) when erroneous responses are induced by presenting incongruent flankers around the target stimulus. The authors report that both the reaction times in the test and the latency of the ERN waves were shorter in the patient group than in a healthy control group. This first study needs to be replicated with a larger sample, but it suggests impaired impulse control and abnormal error-monitoring functioning in persons with heroin dependence and, thus, adds to the literature about cognitive functioning in persons with addictive disorders.

The second original article^[4] uses a rat model to assess the potential ameliorating effects of metformin on the clozapine-induced abnormalities of glucose metabolism. Chinese researchers have been in the forefront of research about the potential benefits of metformin to minimize the risk of the metabolic syndrome in patients treated with second generation antipsychotic medications.^[5] This particular study focuses on clozapine, a commonly used antipsychotic in China that has benefits over other antipsychotics in the treatment of difficult-to-treat patients but, unfortunately, also has a higher risk of inducing the glucose and lipid abnormalities that underpin the development of the metabolic syndrome. The authors administered saline, clozapine, or clozapine+metformin to three groups of rats ($n=6$ in each group) for 28 days, monitored their fasting blood glucose every seventh day, and assessed blood insulin, C-peptide and the expression of glucose transporter-2 (GLUT₂) on the 28th day. The non-significant results support previous findings about increases in blood glucose with administration of clozapine which are reduced with the concomitant administration of metformin. They also found the expected decrease in expression of GLUT₂ with clozapine use, but they did not find that metformin normalized these expression levels. Further studies about the mechanism of action of metformin on antipsychotic-induced blood abnormalities are needed. This information will help identify the appropriate dosage and duration of use of metformin as an adjunctive treatment for patients taking antipsychotic medications who are at high risk of developing the metabolic syndrome.

The third original article^[6] is also about the first known application of a neuropsychiatric test in a particular population; the use of the binocular rivalry test to assess cognitive processing in children with schizophrenia. The binocular rivalry test presents different images to the dominant and non-dominant eyes of respondents

and, thus, can assess both the conscious (image presented to dominant eye) and unconscious (image only presented to the non-dominant eye) processing of information. The authors developed a version of the test to assess the conscious and unconscious processing of social information and compared the results of the test between 15 children with childhood schizophrenia and 15 healthy controls. They found a non-significant increase in the attention the patient group paid to images depicting interpersonal relationships and interpreted this to mean that patients had impairments in the cognitive processing of social information. The use of the binocular rivalry paradigm proved problematic because of the wide variability in the measure used to assess the amount of attention respondents pay to the different types of images; further refinements in the method will be needed to determine its potential utility as a measure of cognitive functioning in patients with schizophrenia.

The last original article^[7] is about the preoperative anxiety and depressive symptoms of cardiac patients who have been admitted to the hospital for a cardiac transplantation. Thirty-eight patients were administered the Hamilton Anxiety scale (HAMA) and the Hamilton Depression scale (HAMD) on admission and then weekly thereafter until they had the transplantation operation. The self-reported anxiety and depressive symptoms increased slightly over the first week of hospitalization. Unlike previous studies in this area, the authors found that anxiety was a much more prominent symptom than depression. There are several possible explanations for this difference, one of which is that these patients were just about to get their operation while previous studies only included patients who were at home on a waiting list for the operation. Interestingly, patients who had been severely ill (i.e., in Stage III cardiac disease) for over a year had *less* prominent anxiety and depressive symptoms than those who had been seriously ill for less than a year, and these differences remained significant after adjusting for all identified confounders. The potential usefulness of such studies is to identify psychological profiles of patients that can predict positive and negative outcomes of the transplantation operations. But patients' depressive and anxiety symptoms can change dramatically over the course of their cardiac disorder as they gradually become more disabled, get on a transplantation waiting list, receive the operation, and enter the prolonged post-operative monitoring and follow-up period. Longitudinal studies will be needed to identify trajectories of psychological symptoms that predict different survival and quality of life outcomes and, thus, require different types of interventions.

The commentary by Caine^[8] is our second commentary about the article on attempted suicides in rural China by Jiang and colleagues.^[9] (The first commentary about this article appeared in the previous issue.^[10]) He suggests that the unique characteristics of suicide attempters identified in the report – the low level of suicidal intent and the low prevalence of psychiatric disorders – also occurs in a subgroup

of suicide attempters in the United States, primarily adolescent girls and young women. The main difference is that in China these suicidal behaviors frequently lead to a fatal outcome because of the common use of toxic pesticides as the suicidal method. Thus, the epidemiological patterning of suicide in China is, indeed, quite different from that in high-income countries, but the characteristics of *suicidal behavior* may be much more similar, with the sole exception of the chosen method. Caine predicts that the demographic pattern of both fatal and non-fatal suicide in China and the relative importance of different suicidal methods will change in parallel with governmental policies aimed at reducing access to the most potent pesticides and with the rapid urbanization of the population. He highlights the need to focus more energy on the monitoring and assessment of *urban* suicidal behavior in China because this will help clarify the role of the massive internal migration on the observed patterns of suicide.

The second Commentary in this issue by Cubells^[11] discusses the meta-analysis on the prevalence of autism spectrum disorders (ASD) in Chinese populations that appeared in the previous issue.^[12] He emphasizes the huge variability in the prevalence of ASD reported from mainland China (from 1.8 to 426.4 per 10,000 individuals) and the methodological flaws evident in the studies identified in the analysis. This casts doubt on the accuracy of the pooled estimate from the studies; the reported prevalence of 12.8 per 10,000 is *much* lower than that reported from high-income countries. Thus the question of whether or not the etiology, prevalence and course of this disabling condition is different in different racial groups, and whether or not the trajectory of the prevalence over time changes in concert with specific environmental changes remains unresolved. As a first step to participating in this high-profile international debate, China urgently needs to upgrade the comprehensiveness and quality of its monitoring system for ASD.

The Case Report in this issue^[13] discusses two cases of probable neuroleptic malignant syndrome (NMS), one of which was fatal, in elderly men taking atypical antipsychotics. Over the last 20 years there has been a dramatic increase in the use of antipsychotic medications with elderly demented patients, particularly in those who have uncontrolled behavioral outbursts. This has helped decrease such outbursts in nursing homes and in private homes where family members manage their elderly relatives, but this environmental improvement has not come without substantial risks. The belief has been that using low doses of atypical antipsychotic medications instead of first-generation antipsychotics substantially reduces the risk of serious side effects, but recent evidence suggests that this may not necessarily be the case. Many elderly patients have compromised liver and kidney function which reduces their ability to metabolize antipsychotic medications and, thus, substantially increases the risk of accumulating toxic levels of antipsychotic medication, even when administered relatively low doses. Moreover, most of these individuals

are treated by non-psychiatric physicians who may not be aware of the clinical manifestations of NMS; and given the rapid progression of the condition, delay in making the NMS diagnosis can, as in one of the cases presented, be fatal. Clearly, educational efforts are needed to improve all clinicians' awareness of the risks associated with the use of antipsychotic medications in elderly individuals.

The biostatistics paper in this issue^[14] provides a comprehensive discussion of the issues related to conducting survival analysis to assess both individual and environmental risk factors for suicide. The paper uses detailed data from the ground-breaking study on suicide prevention in the United States Air Force^[15] to highlight different approaches to conducting survival analyses. It discusses the effect of choosing different starting points for observation (e.g., time of enrollment in the monitoring program, time of entering the target cohort, time of first event of interest, etc.) on the interpretation of identified risk factors. The paper also provides examples of different methods of adjusting results for clustering effects that occur when the observed individuals are selected from specific communities or cohorts.

The Correspondence section includes a letter^[16] that discusses the issue of antidepressant use in adolescents. It supports opinions expressed in our previous Forum on the issue^[17,18] about the importance of antidepressants in the treatment of patients with severe forms of pediatric Major Depressive Disorder (MDD) and in the treatment of less severe forms of pediatric MDD that do not respond to psychosocial interventions alone.

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